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# Russian Eligibility Criteria for Prescribing Menopausal Hormone Therapy to Patients With Cardiovascular and Metabolic Diseases

## Consensus Document of RSC, RSOG, RAE, EUAT, RAP

Menopausal symptoms can impair the life of women at the peak of their career and family life. At the present time, the most effective treatment for these manifestations is menopausal hormone therapy (MHT). The presence of cardiovascular and metabolic diseases in itself does not exclude the possibility of prescribing MHT to relieve menopausal symptoms and improve quality of life. However, often an obstacle to the use of this type of hormone therapy is the fear of physicians to do more harm to patients than good. Caution is especially important when it comes to women with concurrent diseases. Moreover, it should be recognized that there is a shortage of high-quality research on the safety of MHT for underlying chronic non-infectious diseases and common comorbidities. The presented consensus analyzed all currently available data from clinical trials of various designs and created a set of criteria for the appropriateness of prescribing MHT to women with concomitant cardiovascular and metabolic diseases. Based on the presented document, physicians of various specialties who advise menopausal women will receive an accessible algorithm that will allow them to avoid potentially dangerous situations and reasonably prescribe MHT in real-life practice.

*Keywords* Menopausal hormone therapy; cardiovascular diseases; metabolic diseases; diabetes mellitus; venous thromboembolic complications

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## Introduction

The 2023–2030 National Strategy to Support Women was approved by Decree No. 4356 r of the Government of the Russian Federation dated December 29, 2022.

Preserving women's health at any age, improving their quality of life, and increasing the period of active aging is an important task of state policy [1]. An interdisciplinary approach is essential to implement this health care strategy. Internists and obstetrician-gynecologists need to identify women going through menopause in order to provide them with the necessary care in a timely manner.

Climacteric symptoms can disrupt the fabric of live of women at the peak of their careers and family life: 75% of 45–55-year-old women complain of hot flashes; 28.5% of cases of which are moderate to severe; the symptoms may last for 3–15 years [2]. Menopause hormone therapy (MHT) is currently the most effective treatment for such manifestations [3, 4].

The mere presence of cardiovascular and metabolic diseases does not exclude the possibility of ordering MHT to relieve climacteric symptoms and improve the quality of life. However, physicians' fear to bring patients more harm than good is often a challenge to the use of this type of hormone therapy.

Caution is especially important when it comes to women with comorbidities. Moreover, it should be admitted that qualitative studies of MHT safety in major chronic non-communicable diseases and common comorbidities are not enough.

*Thus, the objective of the conciliation document is to:*

analyze all the currently available data from clinical trials with different designs and develop a set of criteria of eligibility for ordering MHT for women with cardiovascular and metabolic comorbidities.

Based on the document presented, physicians of various specialties who advise climacteric women will have an affordable algorithm to avoid potentially dangerous situations and order MHT in real-world practice for a feasible reason.

## Section 1. Basic definitions, symptoms, and classification of menopause

The menstrual cycle is one of the most important indicators of female health and its regularity may vary depending on the stage of reproductive aging.

The Stages of Reproductive Aging Workshop (STRAW) [5] identifies three stages of reproductive aging: reproductive stage, menopausal transition, and postmenopause. The STRAW+10 classification of the stages of the female reproductive aging is presented in Figure 1.1.

Menopausal transition is characterized by irregular menstrual cycles, which reflects the variability of hormonal secretion and ovulatory function.

Menopause is a persistent stopping of menstrual periods; this is the last independent menstruation due to an age-related decrease in hormonal activity and the shutdown of the reproductive function of the ovaries. The date of menopause is estimated retrospectively: after 12 months of amenorrhea [6, 7].

Perimenopause includes the period of menopausal transition + 1 year after the last menstruation.

Perimenopause begins with a disruption of regular menstrual cycles (menopausal transition phase) and lasts up to 1 year after complete stopping of menstrual periods. This phase of reproductive aging can occur in a wide range of age (from 42 to 58 years) and last up to 4–8 years [8].

Postmenopause is the period of life after the last menstrual period.

Climacteric syndrome is a complex of vascular and autonomic dysfunction, mental disturbances, and metabolic and endocrine disorders that occur during progressive or sudden ovarian failure and general aging of the body [9].

The average age of menopause worldwide is 48.8 years (95% CI 48.3–49.2) with significant variations depending on the region of residence [10]; it ranges from 49 to 51 years in the Russian Federation [9]. The prevalence of climacteric symptoms is variable and depends on several circumstances.

Vasomotor symptoms occur more often in the late menopausal transition and are especially pronounced in perimenopause and the first postmenopausal years [11, 12]. Vasomotor symptoms affect up to 80% of perimenopausal women [13]. Sleep disorders occur in 39–47% of perimenopausal women and 35–60% of postmenopausal women [14]. In the Russian Federation, osteoporosis is diagnosed in 34% women aged 50 years and older, and the incidence of prevalence osteopenia is 43% [15].

Vasomotor symptoms and other manifestations of climacteric syndrome not only worsen the quality of



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**Figure 1.1.** Classification of the stages of female reproductive aging (STRAW+10)

Menarche — PM (0)

| Stage | -5 | -4 | -3b | -3a | -2 | -1 | +1a | +1b | +1c | +2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Termino-logy | REPRODUCTIVE PERIOD | | | | TURN OF LIFE | | POSTMENOPAUSE | | | |
| | Early | Meridian | Late | | Early | Late | Early | | | Late |
| | | | | | ***Perimenopause*** | | | | 3–6 years | |
| Duration | *Various* | | | | *Various* | 1–3 years | 2years (1 + 1) | | | *Rest of life* |
| MAIN CRITERIA | | | | | | | | | | |
| Menstrual cycle | Varying or regular nature | Regular | Regular | Minor chan-ges in abun-dance/ duration | Varying duration, stable (7 days and more) fluctuations in the dura-tion of consecutive cycles | Duration of amenor-rhea of 60 days or more | | | | |
| CONFIRMING CRITERIA | | | | | | | | | | |
| *Endocrine*<br>FSH<br>AMH<br>Inhibin B | | | Low<br>Low | Varying*<br>Low<br>Low | ↑Varying*<br>Low<br>Low | ↑>25 IU/L**<br>Low<br>Low | Varying*<br>Low<br>Low | | Stable*<br>Very low<br>Very low | |
| *Number of antral follicles* | | | Low | Low | Low | Low | Very Low | | Very Low | |
| DESCRIPTIVE CHARACTERISTICS | | | | | | | | | | |
| Symptoms | | | | | | Vasomotor symptoms: Likely | Vasomotor symptoms: Very likely | | | Aggra-vation: symp-toms of genito-urinary atrophy |

The STRAW+10 criteria are not applicable in POI, PCOS, after hysterectomy, during COCP, LNG-IUS.

life and limit functional capacity but are also associated with the 1.34-fold risk of coronary artery disease (CAD) and the 1.48-fold risk of any cardiovascular disease (CVD) [16].

Symptoms of the genitourinary syndrome of menopause (GSM) or vulvovaginal atrophy (VVA) develop in 15% perimenopausal women and up to 80% of postmenopausal women [17]. At least one of the VVA symptoms is found in 41% of 50–79-year-old women. The prevalence of urinary disorders (sudden and irresistible urge to urinate, which cannot be suppressed, urinary incontinence) in women depends on the duration of postmenopause and increases from 15.5% in postmenopause lasting for up to 5 years to 41.4% after more than 20 years of postmenopause [17].

*Menopause classification*

By the time of onset, the following are distinguished:

- Premature menopause or premature ovarian failure (under 40 years old),
- Early menopause (40–44 years old),
- Timely menopause (45–55 years old),
- Late menopause (> 55 years).

Natural and iatrogenic (including surgical) menopause is distinguished by the origin.

## Section 2. Indications and contraindications for MHT

Indications and contraindications for MHT are determined by the current clinical guidelines and instructions for use of specific drugs.

*Indications for MHT [4]:*

- Treatment of moderate to severe vasomotor symptoms that significantly reduce the quality of life.
- Treatment of symptoms of GSM, sexual dysfunction.
- Prevention of postmenopausal osteoporosis.
- Replenishment of estrogen deficiency in primary ovarian insufficiency (POI) and early menopause; in bilateral ovariectomy.

*Contraindications for MHT [4]:*

- Genital bleeding of unknown origin.
- Breast cancer (documented, suspected or relevant history).
- Documented or suspected estrogen-dependent malignancies (endometrium, ovaries, uterus).
- History of or current acute and chronic liver diseases (until normalization of liver function tests), including malignant liver tumors.
- History of or current thrombosis (arterial and venous) and thromboembolism (including deep vein thrombosis; pulmonary embolism).
- Myocardial infarction.
- Ischemic or hemorrhagic cerebrovascular disorders.
- Uterine myoma with a submucous node.
- Endometrial polyp.
- Allergy to MHT components.
- Cutaneous porphyria (for the estrogenic component).
- Progestogen-dependent neoplasms (e.g., meningioma) (for gestagens).

## Section 3. Types of MHT and main administration principles

*Systemic MHT*

Systemic MHT is the most effective treatment for vasomotor symptoms and other climacteric manifestations, including GSM. Most MHT agents are approved for the prevention of postmenopausal osteoporosis, with the exception of ultra-low-dose forms.

Table 3.1 presents medicines approved for systemic MHT in the Russian Federation.

*Local MHT*

Local estrogen therapy (estriol) is used in perimenopausal and postmenopausal women with complaints of only GSM symptoms: vaginal dryness, dyspareunia or associated sexual discomfort.

Long-term observations (6–24 months) show no effect of local estrogens on the endometrium, which is why additional administration of progestogens is not required. According to observational studies, local estrogens do not increase the risk of venous thromboembolism complications (VTE), breast cancer (BC), CVDs, endometrial hyperplasia, and cancer [18]. Table 3.2 presents medicines approved for local MHT in the Russian Federation.

*Main principles for MHT administration:*

1. Starting systemic MHT should be considered in women under 60 years and with postmenopause lasting for less than 10 years. Perimenopause and early postmenopause is the most likely time for starting MHT. There are no age restrictions for local estrogens (estriol) therapy of GSM symptoms.
2. The therapeutic goal should be to use the most appropriate minimum effective dose of MHT consistent with treatment goals.
3. MHT is personalized considering risk factors for breast cancer, cardiovascular diseases, osteoporosis, and fractures. Doses and dosage forms, drug composition, modes of administration are chosen considering patient's age, stage of reproductive aging, gynecological diseases (POI (primary/secondary), polycystic ovary syndrome (PCOS), intact uterus/hysterectomy, endometriosis), comorbidities, patient's preferences, and needs.
4. The presence of indications for MHT and the absence of contraindications.
5. The administration of MHT requires periodic dosage adjustments depending on the stage of reproductive aging, age, treatment efficacy and tolerability. It is advisable to reduce MHT doses in older age and longer duration of postmenopause.
6. Treatment monitoring and regular (at least once a year) reassessment of benefit/risk ratio. The duration of therapy is determined by the treatment goal and the benefit/risk ratio.

The safety profile of the MHT components is taken into account. The selection of the minimum effective dosage and method of drug delivery allows personalizing the MHT dosing considering the patient's risk factors (CVDs, risk of breast cancer, risk of osteoporosis, comorbidities, etc.) [14, 15].

Prescribing, correcting, or discontinuing MHT and dynamic monitoring of the treatment efficacy and tolerability is the responsibility of the obstetrician-gynecologist.

## Section 4. MHT in patients with obesity and carbohydrate metabolism disorders

Insulin resistance, dyslipidemia, arterial hypertension, and abdominal obesity are the main markers of


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**Table 3.1.** Drug products approved in the Russian Federation and their combinations for systemic MHT

| | |
|---|---|
| Cyclic estrogen/gestagen combination therapy (perimenopausal) | |
| Fixed combinations (estrogen/gestagen) | |
| Estradiol/dydrogesterone (1 mg/10 mg; 2 mg/10 mg) | |
| Estradiol valerate (2 mg)/levonorgestrel (150 μg) | |
| Estradiol valerate (2 mg)/norgestrel (500 μg) | |
| Estradiol valerate (2 mg)/cyproterone acetate (1 mg) | |
| Free combinations of 2 drugs (estrogen/gestagen) | |
| Estradiol valerate 2 mg | Micronized progesterone 200 mg |
| | Dydrogesterone 10 mg |
| Estradiol hemihydrate transdermal gel 0.6 mg/g | Micronized progesterone 200-400 mg Dydrogesterone 10-20 mg |
| Estradiol hemihydrate transdermal gel 0.1 % – 0.5 g; 1.0 g; 1.5 g | Dydrogesterone 10 mg |
| Continuous monophase estrogen/gestagen combination therapy (postmenopausal) | |
| Fixed combinations | |
| Estradiol/dydrogesterone (0.5 mg/2.5 mg; 1 mg/5 mg) | |
| Estradiol/drospirenone (0.5 mg/0.25 mg; 1 mg/2 mg) | |
| Free combinations of 2 drugs (estrogen/gestagen) | |
| Estradiol valerate 2 mg | Intrauterine system containing micronized levonorgestrel 52 mg (LNG-IUS) |
| Estradiol hemihydrate transdermal gel 0.6 mg/g | Micronized progesterone (100–200 mg) |
| | Intrauterine system containing micronized levonorgestrel 52 mg (LNG-IUS) |
| | Progesterone vaginal gel 8% 90 mg/dose |
| Estradiol hemihydrate transdermal gel 0.1 % – 0.5 g; 1.0 g; 1.5 g | Micronized progesterone (100–200 mg) |
| | Intrauterine system containing micronized levonorgestrel 52 mg (LNG-IUS) |
| | Progesterone vaginal gel 8% 90 mg/dose |
| Other estrogens | |
| Tibolone 2.5 mg | |
| Estrogen monotherapy (after hysterectomy) | |
| Estradiol valerate 2 mg | |
| Estradiol hemihydrate transdermal gel 0.6 mg/g | |
| Estradiol hemihydrate transdermal gel 0.1 % – 0.5 g; 1.0 g; 1.5 g | |

**Таблица 3.2.** Drug products approved in the Russian Federation for topical MHT

| |
|---|
| Estriol (vaginal cream 1 mg/g, vaginal suppositories 0.5 mg) |
| Micronized estriol 0.2 mg/micronized progesterone 2 mg/lactobacilli (vaginal capsules) |
| Estriol 50 μg/g (vaginal gel) |
| Estriol 0.03 mg/lactobacilli (vaginal tablets) |

menopausal metabolic syndrome [19]. Perimenopausal and early postmenopausal women are at a higher risk of insulin resistance compared to the reproductive period [20]. The risk of metabolic syndrome (MS) increases 5-fold in older women. The prevalence of CVDs increases 5-fold in women with carbohydrate metabolism disorders [21].

Obesity, especially abdominal obesity, is closely associated with metabolic syndrome, significantly increases cardiometabolic risk and affects the morbidity, prognosis, and life expectancy of patients [22].

Obesity is an independent risk factor for VTE. The Women's Health Initiative (WHI) randomized study showed a 3-fold increase in the risk of VTE in obese women (BMI >30 kg/m$^2$) compared to women with normal BMI even in the placebo group [23].

For obese patients, it is advisable to order drugs containing progestogens with residual androgenic and glucocorticoid activity, metabolically neutral progestogens should be preferred [24]. After the discovery of the association of mineralocorticoid receptors with the adipose tissue differentiation, the potential role of progesterone and progestins with antimineralocorticoid properties was established in the control of body weight and proliferation of adipose tissue [25]. In a comparative study of combination MHT containing drospirenone or dydrogesterone, patients with menopausal metabolic syndrome showed a significant weight loss after 6 months of treatment [from 74.2 to 72.4 kg in the E/DDH group ($p = 0.03$) and from 74.5 to 72.7 kg in the E/DRSP group ($p = 0.05$)]. Fasting glucose improved in both groups ($p < 0.05$), and HOMA-IR ($p = 0.03$) and MAGE improved in the E/DRSP group ($p < 0.001$) [26].

The incidence of diabetes mellitus (DM) type 2 in the female population is 1.2% at 40–44 years, 2.4% at 45–49 years, 4.2% at 50–54 years, and 9.4% at 55–59 years [27]. Timely initiation of MHT may delay the risk of DM type 2. According to the WHI study, treatment with conjugated equine estrogens (CEE) + medroxyprogesterone acetate (MPA) reduced statistically significantly the incidence of diabetes mellitus type 2 by 19% (HR 0.81; 95% CI: 0.70–0.94; $p = 0.005$), that is a decrease by 16 cases per 10,000 women-years. In the CEE monotherapy cohort, the number of new-onset cases of DM type 2 decreased by 14% (HR 0.86; 95% CI: 0.76–0.98), that is a decrease by 21 cases per 10,000 women-years [28].

According to a meta-analysis of 107 studies, MHT reduces the risk of DM type 2 by 30% (HR 0.7; 95% CI: 0.6–0.9), and with existing diabetes against MHT, fasting glucose and HOMA-IR decrease, the lipid

profile improves, and blood pressure decreases, as well as the degree of abdominal obesity. During estrogen monotherapy or combination MHT, women with DM type 2 had no increase in the risk of cardiovascular mortality [29].

In DM type 2, oral MHT is preferred if there are no contraindications. When ordering combination MHT, it is important consider the metabolic effects of gestagen: progestagens with a neutral effect on metabolic processes should be chosen [30].

The beneficial effect of MHT on carbohydrate metabolism wears off when therapy is discontinued.

Thus, MHT can be considered as a therapy for climacteric symptoms in patients with DM type 2.

The compatibility of hypoglycemic therapy with MHT, levothyroxine sodium (L-T4) replacement therapy, thyrostatic treatment and dopaminergic therapy is reflected in Table 4.1 depending on the routes of administration [31].

**Table 4.1.** Compatibility of MHT and other pharmacological groups in endocrinology

| Drug group | Combination MHT | | Estrogen only MHT | | Tibolone | Topical MHT |
|---|---|---|---|---|---|---|
| | E/G PO | E/G TD | E PO | E TD | | |
| Oral hypoglycemic therapy | 1 | 1 | 1 | 1 | 1 | 1 |
| Insulin therapy | 1 | 1 | 1 | 1 | 1 | 1 |
| L-T4* | 1 | 1 | 1 | 1 | 1 | 1 |
| Thyrostatics | 1 | 1 | 1 | 1 | 1 | 1 |
| Dopamine agonists** | 2 | 2 | 2 | 2 | 2 | 1 |

Digit 1 – this therapy is safe during MHT, there is no contraindications. Digit 2 – this therapy is relatively safe during MHT, titration of one or two components may be required.
* When L-T4 is initiated, its dose may need to be adjusted to prevent atrial fibrillation and osteoporosis.
**MHT does not affect the size of the micro/macroprolactinoma.

*Highlights:*

- Timely initiation of MHT may delay the onset of DM type 2.
- In addition to MHT for obese women, it is recommended to conduct educational conversations in order to correct the usual way of life.
- Oral MHT is preferred for in patients with DM type 2. If there are contraindications for oral administration or an increased risk of thrombosis, transdermal MHT can be used.
- Progestagens with a neutral effect on metabolic processes should be used for women with preserved uterus.
- MHT has a positive effect on the glycemic profile in women with and without DM type 2.

## Section 5. MHT in patients with thrombophilia, venous diseases, venous embolism

### *5.1. Composition of MHT and risk of venous thromboembolic events*

MHT with estrogens is believed to increase the risk of VTE: deep vein thrombosis (DVT) and pulmonary embolism (PE) [32, 33]. However, this effect observed in randomized controlled trials and respective meta-analyses can largely be due to the administration of relatively thrombogenic drugs based on CEE and MPA, and delayed MHT.

Thus, according to the case-control analysis of large databases QResearch and CPRD, the administration of combination MHT including CEE and MPA was associated with the highest risk of VTE. For oral estradiol, a significant increase in the risk of VTE was noted, and the effect was dose dependent. At the same time, the combination of oral estradiol and dydrogesterone did not increase the risk of VTE neither in cyclic nor monophasic combination regimens of MHT, whatever the dose of estradiol was used. Administration of transdermal estradiol, both as monotherapy and as a part of combination MHT, was not associated with an increased risk of VTE. Irrespective of BMI, the combination of oral estradiol and dydrogesterone, transdermal estradiol, both as monotherapy and in combination with gestagen, was not associated with an increased risk of VTE. In the cohort of women with history of VTE episodes and/or who received anticoagulant therapy, there was a significant reduction in the risk of VTE during transdermal estradiol monotherapy, no increase in the risk of VTE during the combined use of transdermal estradiol with gestagen and oral estradiol with dydrogesterone [34].

In the observational studies, the risk of VTE did not increase during the monotherapy with low-dose (<50 μg/day) and higher-dose transdermal estradiol and the combined used with gestagen in cyclic or continuous regimens [34–37]. On the one hand, there is evidence that transdermal estrogen is associated with a lower risk of VTE than its oral forms, on the other hand, the


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absence of differences was suggested [34, 35, 38–40]. There are no proper randomized controlled or other clinical trials comparing these approaches.

Large real-world clinical study EURAS-HRT (more than 30,000 women) confirmed the long-term safety profile of drospirenone-containing MHT for VTE. The risk of VTE during MHT with drospirenone was comparable, and the risk of serious arterial thromboembolism (mainly acute myocardial infarction and ischemic stroke) was significantly lower than when taking another MHT (there was no detailed comparison of the composition and characteristics of the other MHT) [41].

In general, the modern low-dose and ultra-low-dose combined oral MHT using estradiol appears to be safe for VTE and comparable to transdermal MHT in terms of the risk of venous thrombosis [34, 40]. However, the assessment of the benefit-risk ratio of MHT, the choice of a drug, its composition, and the route of administration should be carried out individually given the clinical picture and the presence of risk factors for VTE.

The case-control analysis of large QResearch and CPRD databases showed no increase in the risk of VTE for tibolone [34].

Local therapy for GSM symptoms with estradiol does not increase the risk of venous thrombosis and can be used in all categories of patients [31].

LNG-IUS containing micronized levonorgestrel 52 mg can also be used as a component of MHT. According to the studies, the administration of LNG-IUS did not increase the risk of VTE [41, 42].

It should be kept in mind that, when deciding on the possibility and composition of MHT, the risk of VTE cannot be considered separately from other thrombotic risks. So, even when a slight increase in the risk of VTE is not excluded, this effect can be reduced by a decrease in the incidence of arterial thrombosis and other cardiovascular complications, which will ultimately have a neutral or positive effect on mortality [32, 43, 44].

### *5.2. MHT in various clinical situations associated with thrombosis*

#### *Venous thrombosis*

MHT is contraindicated in acute DVT and/or PE.

Most experts recommend abandoning MHT in female patients with history of VTE [31, 45, 46]. There is evidence of no increase in the risk of recurrent VTE when administering transdermal MHT during anticoagulant therapy, however, there are limited data on the safety of this approach after VTE [37, 39].

In severe climacteric symptoms, the lowest effective dose of transdermal estradiol (< 50 μg/day) or ultra-low-dose (estradiol 0.5 mg) oral combination MHT can be used with appropriate anticoagulant therapy in addition to local estrogens [36, 37, 45, 46]. It is also not excluded that modern MHT is safe enough after the scheduled cessation of anticoagulant therapy in certain categories of patients at a low risk of recurrent venous thrombosis [37].

The available data do not allow us to unambiguously judge the risk of MHT in acute superficial vein thrombosis (SVT) and history of SVT [47]. The decision on the possibility of using modern oral and transdermal MHT in SVT should be made individually considering the characteristics of the clinical situation, the presence of risk factors for VTE, and the history of SVT as labeled contraindications of a particular drug.

In the studies assessing the risk of DVT and/or PE after SVT, thrombosis of non-varicose and varicose superficial veins (varicose vein thrombophlebitis) was not distinguished. Varicose vein thrombophlebitis is primary due to the presence of varicose veins, which can be eliminated long before the administration of MHT.

History of varicose vein thrombophlebitis should be considered a restriction for MHT if there with is a direct indication of SVT history as a labeled contraindication of a specific drug for MHT.

#### *Varicose veins*

The presence of varicose veins is not a contraindication for MHT and should not affect the decision to prescribe MHT. There is no evidence that MHT increases the risk of varicose vein thrombosis/thrombophlebitis. Ultrasound examination of the lower limb veins is not required before prescribing MHT.

#### *Thrombophilia*

There are very few data on the safety of MHT in antiphospholipid syndrome [39]. Oral and transdermal MHT is not recommended in patients with antiphospholipid syndrome due to the high risk of venous and/or arterial thrombosis. It potentially could be used in women with low disease activity or asymptomatic changes in individual laboratory parameters that do not have additional risk factors for thrombosis [47].

There are limited data on the safety of MHT in asymptomatic thrombophilia. Several studies established an increased risk of VTE in oral MHT during some types of thrombophilia (protein C deficiency,

protein S deficiency, antithrombin deficiency, factor V Leiden, prothrombin G20210A gene mutation, high levels of coagulation factor VIII) [48, 49]. However, this is not enough to explicitly prohibit oral MHT during asymptomatic thrombophilia, more research is required into this matter.

The decision on the possibility and composition of MHT should be made individually, considering the information about the presence of documented asymptomatic thrombophilia, the severity of climacteric symptoms, the presence of additional risk factors for VTE, and the indication of certain types of thrombophilia as a labeled contraindication of a specific drug for MHT. [31, 40, 50]. Screening for thrombophilia before starting MHT is not recommended.

Family history of thrombosis (venous or arterial thrombosis in relatives of the 1st degree relatives under 50 years) is indicative of an increased risk of VTE but is not a reason for prohibiting MHT [17, 37, 50].

Transdermal MHT was reported to not increase the risk of VTE in women with asymptomatic thrombophilia, but evidence of its safety in this clinical setting is limited [37, 39, 49].

Documented family history of thrombosis and/or the presence of certain types of thrombophilia as a labeled contraindication is a limitation for the use of a particular drug.

### *5.3. MHT in surgical procedures and hospitalization with acute non-surgical disease*

Currently, there is no evidence of benefit from discontinuing MHT before surgery or during hospitalization for acute non-surgical disease (except for those in which MHT is contraindicated) [51]. Preventive anticoagulants at an increased risk of VTE neutralize the potential prothrombotic effect of hormonal drugs. When stratifying the risk of VTE in such patients, continuation of MHT is recommended to be considered as an additional risk factor for VTE.

## Section 6. MHT in female patients with atherosclerotic cardiovascular diseases

In 1998, the HERS study (the first randomized, placebo-controlled study of hormone therapy (HT) with estrogens and progestin for the secondary prevention of coronary artery disease (CAD) in postmenopausal women with documented CAD) found no benefit of HT in terms of cardiovascular complications and all-cause mortality. The results of this study are an argument against initiating HT for the secondary prevention of CAD [52].

A more recent meta-analysis of 19 randomized controlled trials including 40,410 postmenopausal women receiving MHT (oral in most cases) found no significant increase in all-cause mortality, cardiovascular mortality, or MHT-related MI in either primary or secondary prevention of cardiovascular events.

Subanalysis based on the timing of MHT initiation showed that:

- mortality was lower (HR 0.70; 95% CI: 0.52–0.95) and there were fewer cardiovascular events (a combination of cardiovascular death and non-fatal MI) among women who started MHT within 10 years after menopause (HR 0.52; 95% CI: 0.29–0.96) [33];
- the risk of stroke increased without any effect on mortality or other CVD outcomes in women who started MHT >10 years from the onset of menopause [33].

Currently, MHT is not recommended for women with CAD, including angina pectoris, [40], and myocardial infarction is a contraindication to MHT.

The manifestation of CAD during MHT usually implies its cancellation. Although the authors of the mentioned above HERS study concluded that, given the favorable picture of ischemic events after several years of MHT, it may be advisable for women with CAD who already receive this treatment to continue it [52]. A meta-analysis that included 5,766 patients with the present CVDs showed that the absolute risk of death, MI, angina pectoris, or revascularization in this category of patients was low during MHT (Table 6.1). Thus, female patients with CAD onset during treatment who are set up for the continuation of MHT. It should be decided individually together with a cardiologist and a gynecologist whether the treatment should be canceled [33].

It is advised to avoid systemic MHT for female patients with a history of stroke and alternative (non-hormonal) treatment should be considered. In the WHI study, an increased risk of ischemic stroke was noted in the combination MHT group (HR 1.37; 95% CI: 1.07–1.76) and in the estrogen monotherapy group (HR 1.35; 95% CI: 1.07–1.70), regardless of the patient's initial risk [53, 54]. In a meta-analysis of 4 studies including 719 female subjects without cardiovascular disease, the risk of stroke was increased (HR 1.32; 95% CI: 1.12–1.56) compared to placebo. A meta-analysis of studies performed as part of secondary prevention of CVDs (a total of 5,172 subjects from 5 studies) showed a trend of increasing risk of stroke (Table 6.1) [33].


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**Table 6.1.** The risk of cardiovascular complications and death during hormone therapy in postmenopausal patients with cardiovascular diseases (a meta-analysis of randomized controlled trials)

| Results | Secondary prevention |
|---|---|
| All-cause death | HR 1.04 (95 % CI: 0.87–1.24) |
| Cardiovascular death | HR 1.00 (95 % CI: 0.78–1.29) |
| Myocardial infarction | HR 0.98 (95 % CI: 0.81–1.18) |
| Angina pectoris | HR 0.91 (95 % CI: 0.74–1.12) |
| Revascularization | HR 0.98 (95 % CI: 0.63–1.53) |
| Stroke | HR 1.09 (95 % CI: 0.89–1.33) |

Non-atherosclerotic/non-thrombotic CAD is more common in women, but there is currently insufficient data to stratify the risk for MHT by disease subtypes. An individual approach to the administration of MHT is required for 50–59-year-old women with a history of MI without obstructive coronary arteries, spontaneous coronary artery dissection, coronary microvascular dysfunction, or coronary vasospasm. It is recommended to avoid systemic MHT during spontaneous dissection of the coronary arteries due to the alleged pathophysiological relationship with the levels of female sex hormones. This recommendation is based on the fact that >90% of patients with spontaneous coronary artery dissection are female.

Local estriol can be used for the symptoms of GSM in women with cardiovascular diseases, [4, 18, 55]. It should be noted that local estrogens and as estrogens for systemic MHT have the same labeled contraindications. This warning is not based on scientific research data but is associated with international requirements for the mandatory indication of common contraindications for the drug regardless of the modes of administration [45]. Local estriol has minimal systemic absorption and is not metabolized to the more active forms of estrogens (estradiol and estrone), and the levels of circulating estriol, estradiol, and estrone remain normal for postmenopause [56, 57]. Several large observational studies confirmed the absence of an increased risk of adverse health effects, including CVDs, VTE, and cancer, when local MHT with estriol is used [58, 59].

*Highlights*

- MHT is not recommended for patients with coronary artery disease, and patients with cerebrovascular accident or transient ischemic attack. Non-hormonal therapy should be used to treat vasomotor symptoms in these patients.
- For patients who develop CAD during MHT and are set up to continue it, the issue of discontinuing MHT should be resolved individually by a consensus of a cardiologist and a gynecologist.

## Section 7. MHT in female patients with cardiovascular risk factors

### *7.1. Dyslipidemia*

Clinical studies showed that MHT, compared to placebo or no treatment, can significantly increase the levels of high-density lipoprotein cholesterol (HDL–C) and reduce the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), and liprotein (a) (Lp (a)) [60–62]. It should be noted that Lp (a) is an independent cardiovascular risk factor and a risk factor recurrent ischemic stroke in particular [63, 64]. Statin therapy has little effect on the levels of this pro-atherogenic lipoprotein, and MHT significantly reduces it [65]. There are controversial data on the effect of MHT on triglyceride (TG) levels. In some studies, a significant increase in TG levels is shown [66], and there was no significant difference in the TG levels between the two groups receiving placebo and MHT in other studies [61, 67–75].

MHT is generally associated with favorable changes in lipid parameters in postmenopausal women in both short term and long term. However, there are characteristics associated with drug doses and modes of administration.

Oral MHT was shown to increase TG levels compared to transdermal MHT [62]. A moderate but significant increase in triglyceride levels, even during therapy with fenofibrate and/or polyunsaturated fatty acids, can have a clinically significant effect on the progression of atherosclerosis and the development of pancreatitis. Thus, transdermal or low-dose MHT or tibolone is a safer choice for women with hypertriglyceridemia.

At the same time, oral MHT is associated with a positive effect on the levels of LDL–C, and the concentration of this pro-atherogenic factor has the greatest effect on the development of atherosclerosis and destabilization of atherosclerotic plaques.

It is still unclear whether low-dose MHT can have the same effect on the lipid profile as standard MHT doses. It was found in one study that low-dose MHT was associated with higher levels of TC and LDL–C and lower levels of TG compared to the standard doses [76]. Other studies showed a similar benefit for TG in the group of low-dose estrogen MHT but found no significant differences in TC and LDL–C levels between the two groups (high and low doses).

Moreover, low-dose estradiol MHT was found to reduce HDL–C levels. Epidemiologically low plasma

HDL–C was associated with an increased risk of ischemic CVDs [77]. Taken together, the benefits of low-dose MHT and transdermal estradiol for the lipid profile may be limited only by the TG levels.

There are controversial data on the effect of tibolone on the lipid profile. A meta-analysis (2021) showed that tibolone reduced TC, HDL–C, and TG. LDL–C levels are significantly decreased if tibolone is administered for ≥ 26 weeks [78]. There was no difference between conventional MHT and tibolone with regard to the effect on Lp (a) [79].

There is evidence of an increased risk of CAD in patients who received estrogen-gestagen combination therapy, but not in patients who received estrogen monotherapy [80]. Unfortunately, the lipid profile was not assessed depending on the type of progestogen used in either large-scale RCT. One observational study showed that the addition of progestogens attenuates the benefits of estrogen for the lipid profile [81], and a meta-analysis (2017) showed that there was no significant difference in the Lp (a) decrease [79].

Although the results of several studies demonstrated a positive effect of MHT on the lipid profile, it should be emphasized that MHT is not recommended for the treatment of dyslipidemia and reducing the risk of cardiovascular diseases [82].

*Highlights*

- MHT has a positive effect on the lipid profile in peri- and postmenopausal women.
- MHT is not recommended as a therapy for dyslipidemia since changes in the lipid profile during MHT are minimal and not comparable to the effects of lipid-lowering therapy.
- Oral MHT is more effective in lowering LDL–C than transdermal MHT.
- Transdermal or low-dose MHT or tibolone is a safer choice for women with hypertriglyceridemia.

### *7.2. Arterial hypertension*

Female-specific risk factors for arterial hypertension (AH) and CVDs in later life include menarche timing, history of menstrual and reproductive disorders, uterine fibroids, polycystic ovary syndrome, endometriosis, adverse pregnancy outcomes, premature ovarian failure, and menopause. An increased risk in the reproductive period of life may contribute to a more significant increase in the risk of peri- and postmenopausal CVDs [83–87].

In AH, as well as in other diseases, sex-related and gender differences are distinguished, which affect epidemiology, pathophysiology, and clinical management.

In 2019, the age-standardized prevalence of AH (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or antihypertensive therapy) was 32% in women worldwide [88]. In Eastern Europe, the prevalence of AH ranged between 34% and 46% in women aged 30–79 years [88]. The prevalence of AH increases with age [89] but has a more pronounced tendency to decrease before menopause compared to men of the same age, with a pronounced increase in postmenopausal women [14]. The prevalence of AH after 65 years is higher in women than in men [88–90].

The BP trajectories during life in men and women are explained by differences in the mechanisms of BP regulation, a combination of sex-related and gender factors [88, 89]. In premenopausal women, estrogens contribute to lower blood pressure in the context of their global vasoprotective effect. Protection is mediated by various mechanisms, including endothelial vasodilation by enhancing the nitric oxide production pathway and inhibiting the activities of the sympathetic nervous system and renin-angiotensin system. Moreover, estrogens reduce endothelin production, oxidative stress, and inflammation [87]. Cessation of ovarian function due to natural aging or medical interventions is associated with an increased burden of cardiometabolic risk factors, including weight gain, elevation of plasma glucose and cholesterol levels and BP, which leads to an increased cardiovascular risk [86, 87, 91, 92]. After menopause, a pronounced decrease in estrogen levels partly explains increased BP and the risk of AH [87, 88]. Also, due to a sharp decrease in progesterone (a natural antagonist of aldosterone), the renin-angiotensin-aldosterone system (RAAS) is reactivated with consequent fluid retention and increased BP [93].

The following female-specific pathophysiological characteristics of AH are distinguished [94]:

- Close relationship between obesity and AH;
- Relation of gynecological disorders (anovulation, proliferative gynecological diseases) and unfavorable course of pregnancy (preeclampsia, gestational diabetes mellitus) with cardiometabolic risk and AH;
- Cardiovasoprotective effect (including vasodilating) of the estrogen level physiological for the reproductive age;
- Pharmacological use of estrogen in the presence of endothelial dysfunction can contribute to higher BP and the cardiovascular risk, the administration of


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exogenous estrogens in dosages used for MHT has no adverse effect on BP;
- Progesterone contributes to leptin-mediated endothelial dysfunction in obese premenopausal women;
- More pronounced sensitivity to sodium;
- Higher incidence of inflammatory diseases associated with AH and CVDs.

Faster increase in arterial stiffness is observed in postmenopausal women (compared to men of the same age). Older women have higher aortic stiffness than men, which apparently contributes to the onset of isolated systolic AH, uncontrolled AH, heart failure with preserved left ventricular ejection fraction, aortic stenosis, which is more common among women [95, 96].

Menopause was found to double the risk of AH even after adjusting for age and body mass index [97]. Although MHT contains estrogens, there is no convincing evidence that BP will increase significantly in menopausal women with or without AH [98]. However, after starting of MHT, regular BP monitoring should be recommended to confirm continuous normal BP or control BP during antihypertensive therapy [99, 100]. MHT should be discontinued in case of uncontrolled AH. It is advisable to decide on discontinuing MHT together with a cardiologist.

*Highlights*
- MHT can be started subject to BP control
- MHT is not administered for primary or secondary cardiovascular prevention.

### *7.3. Smoking*

Smoking significantly increases the risk of arterial cardiovascular events and is a risk factor for malignancies.

Smoking is not a risk factor for VTE in MHT (including combined oral MHT). Despite the fact that smoking is not a reason for refusal of MHT, including combined oral drugs, oral MHT should be prescribed with caution to smokers; they should be informed about the health risks associated with smoking and urged to quit smoking [23, 101, 102].

*Highlights*
- It is necessary to inform women about the health risks associated with smoking and insist on quitting.
- The decision on the possibility of using MHT should be made for women who smoke considering the whole element of risk.

## Section 8. MHT in special clinical situations

### *8.1. Peripheral atherosclerosis*

The prevalence of peripheral arterial atherosclerosis is 4.89%, 5.73%, and 6.73% among 45–49-, 50–55-, and 56–60-year-old women, respectively. Menopause increases 2-fold the risk of carotid atherosclerosis [103]. Premature and early menopause are associated with higher volume and prevalence of atherosclerotic plaques [104].

Estrogen monotherapy in postmenopausal women reduces the risk of peripheral arterial atherosclerosis by 52% within a year, which was shown in the observational Rotterdam study [105]. In the HERS and HERS II RCTs, combined oral MHT did not provide a statistically significant reduction in the number of events associated with peripheral arterial atherosclerosis in patients with coronary artery disease [52, 106]. It was determined in an observational study that MHT, whatever is chosen, reduces the risk of peripheral arterial atherosclerosis by 20% [107]. A descriptive review by Davies RS et al. discusses a decrease in the levels of circulating LDL cholesterol, an increase in HDL cholesterol, and a positive effect on endothelial function as a mechanism of the positive effect of MHT on the course of peripheral atherosclerosis [108].

### *8.2. Chronic heart failure*

According to the population-based study EPOCH-CHF, the prevalence of CHF is 12.2% and 26.2% in 50- and 60-year-old Russian women, respectively, mainly with preserved left ventricular ejection fraction (LVEF) [109]. The five-year survival rate for CHF patients is ≤ 50% [110].

Early menopause increases the risk of CHF by 33% as shown in a meta-analysis of three observational studies [111].

It was found in an RCT after 10 years of treatment that women receiving oral estrogen or combination MHT prescribed within a mean of 7 months after menopause faced a significantly lower risk of death, CHF, myocardial infarction without any increase in the risk of cancer, VTE, or stroke [112].

Oral estrogen and combination MHT in female patients of 50 years and older with CHF class III–IV and non-ischemic LVEF < 35% provided a statistically significant reduction in the risk of all-cause mortality by 40%, as was shown in the BEST RCT (Beta-Blocker Evaluation of Survival Trial) subanalysis [113].

Subanalysis of the WHI (Women's Health Initiative) RCT showed that oral estrogen monotherapy and

combination MHT did not increase the risk of hospitalizations associated with CHF, regardless of LVEF and a woman's age when prescribing MHT [114].

### *8.3. Atrial fibrillation*

The prevalence of atrial fibrillation (AF) is lower in women of all age groups compared to men, but all-cause mortality is higher in women: AF is independently associated with a 2 fold risk of death in women compared to a 1.5 fold risk of death in men [115]. In the ATRIA observational study, the annual incidence of thromboembolic complications among AF patients not taking warfarin was 3.5% in women compared to 1.8% for men [116]. Women with additional risk factors for stroke, especially in older age (>65 years), face a greater risk of stroke even if they receive anticoagulant therapy, and the risk of bleeding during anticoagulation was the same for female and male patients [117]. Women with AF have more pronounced symptoms and severity of stroke. In clinical practice, women with AF are less likely to receive specialized care, a more conservative approach is more often used [118, 119].

Menopause increases the risk of AF by 82% [120].

The European observational BiomarCaRE Consortium study showed that the prevalence of AF was 4.4% in postmenopausal women (mean age 49.2 years), which was correlated with an increase in the risk of stroke by 42% of myocardial infarction by 78%, and of the mortality increased more than 3.5-fold [121].

According to the WHI RCT subanalysis and observational studies, combination MHT, oral estrogen monotherapy, and tibolone increase the risk of AF [120, 122–124].

The contribution of transdermal and local estrogens to the development of AF in women during menopause is not known.

### *8.4. Valvular heart disease*

The possibility of prescribing oral MHT in perimenopausal and postmenopausal women with valvular heart disease is determined by the presence of complications:

- MHT is contraindicated in AF and blood clots in heart chambers;
- MHT can be prescribed by an interdisciplinary team in non-ischemic CHF without complications [125].

## Conclusion

- Indications and contraindications for MHT are determined by the current clinical guidelines and instructions for use of specific drugs.
- A set of acceptance criteria for prescribing menopausal hormone therapy to patients with cardiovascular and metabolic diseases is provided in Appendix 1 (see additional materials on the journal website).
- The following categories were defined in accordance with the WHO international nomenclature to unify the recommendations [31]:

CATEGORY 1 – no restrictions for MHT;
CATEGORY 2 – benefits of MHT outweigh the risks;
CATEGORY 3 – possible risks outweigh benefits;
CATEGORY 4 – MHT is not recommended.

- When a woman complains of hot flashes, sweating, palpitations, an internist should conduct a survey to identify the relationship of complaints with possible climacteric disorders. The survey should include information about the date of the last spontaneous menstruation, menstrual irregularities, and current use of hormonal birth control or MHT. If relation of complaints with climacteric disorders is suspected, the patient should be referred to an obstetrician-gynecologist.
- An obstetrician-gynecologist prescribes MHT, corrects doses, changes drugs, discontinues treatment, conduct annual dynamic monitoring of treatment efficacy / tolerability, updates treatment goals, and assesses the benefit / risk ratio (see Appendices 2 and 3 in additional materials on the journal website).
- If MHT adverse events are detected / suspected by a non-gynecologist physician, the patient should be advised to consult an obstetrician-gynecologist.
- If cardiovascular risk factors, cardiovascular and metabolic diseases are detected / suspected by an obstetrician-gynecologist, the patient should be advised to consult an internist.

## List of Abbreviations

AH, arterial hypertension
BP, blood pressure
AMH, anti-Müllerian hormone
ASP, atherosclerotic plaque
VVA, vulvovaginal atrophy
IUS, intrauterine system
VTE, venous thromboembolism including deep vein thromboembolism and / or pulmonary embolism
G, gestagens
HT, hormone therapy
GSM, genitourinary syndrome of menopause
DBP, diastolic blood pressure
CI, confidence interval
DYD, dydrogesterone


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DRSP, drospirenone
PAD, peripheral artery disease
E, estradiol
CAD, coronary artery disease
MI, myocardial infarction
CEE, conjugated equine estrogen
CS, climacteric syndrome
LNG, levonorgestrel
Lp (a), lipoprotein (a)
DP, drug product
MHT, menopausal hormone therapy
MP, micronized progesterone
MPA, medroxyprogesterone acetate
MS, metabolic syndrome
NA, not applicable
NSAID, nonsteroidal anti-inflammatory drug
ACS, acute coronary syndrome
CVA, cerebrovascular accident
HR, hazard ratio
POI, premature ovarian insufficiency
PO, per os
DOAC, direct oral anticoagulant
RCT, randomized clinical trial
BC, breast cancer
SBP, systolic blood pressure
DM, diabetes mellitus
PCOS, polycystic ovary syndrome
CVD, cardiovascular disease
SE, systemic embolism
TG, triglyceride
DVT, deep venous thrombosis
TD, transdermal
TIA, transient ischemic attack
SVT, superficial vein thrombosis (thrombophlebitis) including thrombosis of varicose and non-varicose superficial veins
PE, pulmonary embolism
LVEF, left ventricular ejection fraction
AF, atrial fibrillation
FSH, follicle stimulating hormone
CKD, chronic kidney disease
HDL, high density lipoprotein
LDL, low density lipoprotein
CHF, chronic heart failure
E, estrogen
HOMA-IR, Homeostasis Model Assessment of Insulin Resistance
MAGE, mean amplitude of glycemic excursions

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# Russian Eligibility Criteria for Prescribing Menopausal Hormone Therapy to Patients With Cardiovascular and Metabolic Diseases

Consensus Document of RSC, RSOG, RAE, EUAT, RAP

## ADDITIONAL MATERIALS

**Annex 1.** Eligibility criteria for the administration of MHT

| | Combination MHT | | Estrogen monotherapy | | Tibolone | Topical MHT | Notes |
|---|---|---|---|---|---|---|---|
| | Oral | Transdermal | Oral | Transdermal | | | |
| **Carbohydrate metabolism disorders** | | | | | | | |
| DM | 1 | 1 | 2 | 1 | NA | 1 | |
| **Venous thrombosis and/or PE** | | | | | | | |
| Acute DVT/PE | 4 | 4 | 4 | 4 | 4 | 1 | Acute DVT/PE is a period requiring the use of a full therapeutic dose of an anticoagulant (the main phase of anticoagulant therapy, the first 3–6 months). |
| History of DVT/PE | 4 | 3 | 4 | 3 | 4 | 1 | Transdermal or ultra-low-dose oral MHT may be considered for severe symptoms of menopause during anticoagulant treatment in some patients; MHT should not be used after canceling anticoagulants in most cases |

| | Combination MHT | | Estrogen monotherapy | | Tibolone | Topical MHT | Notes |
|---|---|---|---|---|---|---|---|
| | Oral | Transdermal | Oral | Transdermal | | | |
| Superficial vein thrombosis (acute process or history) | 3 | 3 | 3 | 3 | NA | 1 | |
| **Non-thrombotic chronic venous diseases** | | | | | | | |
| Non-thrombotic chronic venous diseases (varicose veins, reticular veins, leg telangiectasia | 1 | 1 | 1 | 1 | 1 | 1 | |
| **Thrombophilia** | | | | | | | |
| Asymptomatic thrombophilia with a high risk of VTE (protein S deficiency, protein C deficiency, antithrombin deficiency, ffactor V Leiden, prothrombin G20210A gene mutation, elevated coagulation factor VIII) | 3 | 2 | 3 | 2 | NA | 1 | Documented thrombophilia should be considered, no routine examination for thrombophilia is required before prescribing MHT. The presence of documented asymptomatic thrombophilia, severe menopausal symptoms, additional risk factors for VTE, and the indication of specific types of thrombophilia in the list of labeled contraindications for a particular drug for MHT should all be taken into consideration when determining the possibility and composition of MHT. Transdermal drugs for MHT, according to available data, do not increase the risk of venous thrombosis in patients with asymptomatic thrombophilia. |
| Antiphospholipid syndrome | 4 | 3 | 4 | 3 | 4 | 1 | The possibility of MHT is not excluded in women with low or moderate disease activity who do not have additional risk factors for venous thrombosis |
| Family history of thrombosis | 2 | 2 | 2 | 2 | 2 | 1 | The presence of a first-degree relative with history of venous or anterior thrombosis before the age of 50 years. |
| **Surgical interventions and acute non-surgical diseases with hospitalization** | | | | | | | |
| Surgical intervention | 1 | 1 | 1 | 1 | 1 | 1 | It is necessary before surgery to assess the risk of DVT/PE in the postoperative period according to the Caprini score. When determining the likelihood of developing postoperative DVT/PE, it is advised to consider MHT as an extra point on the Caprini score. It is not required to discontinue MHT for surgical interventions. Prevention of venous thrombosis with anticoagulants should be carried out in accordance with the risk category for DVT/PE as determined using the Caprini score. |
| Acute non-surgical diseases requiring hospitalization | 1 | 1 | 1 | 1 | 1 | 1 | When patient is hospitalized, the risk of DVT/PE should be assessed using the recommended scores (e.g., Padua score). When determining the likelihood of developing postoperative DVT/PE, it is advised to consider MHT as an extra point. It is not required to discontinue MHT in acute non-surgical diseases requiring hospitalization if they are not contraindicated. Prevention of venous thrombosis with anticoagulants should be carried out in accordance with the established risk category for DVT/PE. |
| **Atherosclerotic cardiovascular diseases** | | | | | | | |
| CAD | 3 | 3 | 3 | 3 | NA | 1 | MHT is not recommended in CAD A cardiologist and a gynecologist should collaborate to assess whether to cancel MHT in patients who develop coronary artery disease during therapy and are set for continuing it. |
| Myocardial infarction (acute or history of) | 4 | 4 | 4 | 4 | 4 | 1 | |
| Cerebrovascular accident including transient ischemic attack (acute or history) | 4 | 4 | 4 | 4 | 4 | 1 | |


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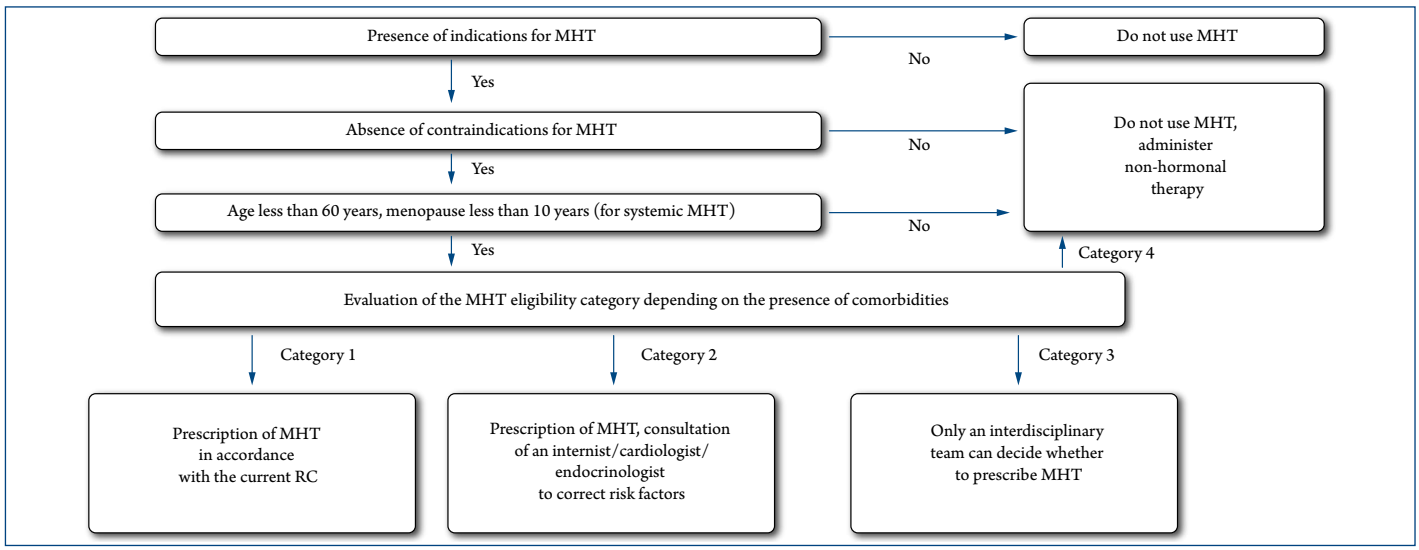
| | Combination MHT | | Estrogen monotherapy | | Tibolone | Topical MHT | Notes |
|---|---|---|---|---|---|---|---|
| | Oral | Transdermal | Oral | Transdermal | | | |
| **CVD risk factors** | | | | | | | |
| Hyperlipidemia (except for hypertriglyceridemia) | 1 | 1 | 1 | 1 | 1 | 1 | |
| Hypertriglyceridemia | 3 | 2 | 3 | 2 | 2 | 1 | MHT is not recommended in TG > 4.5 mmol/L, TG should be corrected. |
| Arterial hypertension | 1 | 1 | 1 | 1 | 1 | 1 | MHT can be started subject to BP control. |
| Smoking | 2 | 2 | 2 | 2 | NA | 1 | For smokers, special attention should be paid to the totality of risk factors, and thus decisions should be made individually. |
| **Other diseases/conditions** | | | | | | | |
| Peripheral atherosclerosis | 2 | 2 | 2 | NA | NA | NA | |
| Chronic heart failure (nonischemic origin) | 2 | 2 | 2 | NA | NA | NA | |
| Atrial fibrillation | 4 | 4 | 4 | 4 | 4 | NA | |

Category 1 – no restrictions on MHT; category 2 – benefits outweigh risks; category 3 – risks generally outweigh benefits; category 4 – MHT should not be used. NA – not applicable due to lack of data.

## **Annex 2.** Algorithm for deciding whether MHT should be administered




## **Annex 3.** Algorithm for deciding whether MHT should be canceled